8EHQ-0303-15225

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Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, D.C. 20460

Dear 8(e) Coordinator:

8EHQ-02-15225

This letter is to inform you of the results of a recently completed rat developmental toxicity study with the above referenced test substance.

Groups of 22 time-mated Crl:CD®(SD)IGS BR rats were dosed with oxydianiline once daily by gavage at dose levels of 0, 3, 10 or 30 mg/kg/day over days 6-20 of gestation (day 6-20G). The vehicle was polyethylene glycol (PEG 400) and the dose volume was 4 ml/kg/day. During the in-life portion of the study, maternal body weights, food consumption, and clinical signs data were collected. On day 21G, dams were euthanized and subjected to a gross external and internal examination. Uterine contents were described; all fetuses were removed and individually weighed, sexed, and examined for external alterations. Approximately one-half of the fetuses were subjected to visceral and head evaluations; all fetuses were examined for skeletal alterations.

There was no test substance-related maternal mortality nor were there any test substance-related maternal gross postmortem findings. Maternal toxicity was observed at 30 mg/kg/day and included statistically significant, test substance-related reductions in maternal body weights and/or weight changes, and food consumption. Clinical observations included alopecia and stained fur at 30 mg/kg/day. Non-adverse effects on body weight gain and food consumption were observed at 10 mg/kg/day.

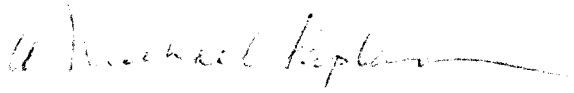
There was a test substance-related reduction (8% lower than control mean) in mean fetal weight at 30 mg/kg/day. There was a statistically significant reduction in mean fetal weight at 3 and 10 mg/kg/day (5.24, 5.22 vs. 5.43 g. for the control group) that was not considered test substance-related due to the lack of a dose-response and the small magnitude of the change (3-4% lower than control mean). Malformations observed in three fetuses from three litters in the 30 mg/kg/day group (one septal defect; one right-sided aortic arch and septal defect; and one umbilical cord hernia) were not considered test substance-related because the incidence was low, and was within the laboratory's historical control range with regard to septal defects. Therefore, there were no test substance-related fetal malformations observed at any dose level. For perspective, malformations were also observed in one fetus in the control group (imperforate anus and short tail).

There was a test-substance-related statistically significant increase in the incidence of fetal variations (supernumerary ribs) at 30 mg/kg/day that was consistent with the reduction in mean fetal body weight at this dose level. Pale liver was observed in 6 fetuses from 4 litters in the 30 mg/kg/day group, and was considered possibly test substance-related. There was a significant increase in the incidence of patent ductus arteriosis at 30 mg/kg/day (2 affected fetuses from 2 litters). Although statistically significant, this finding was not considered to be toxicologically relevant because the incidence was within the range of relevant historical control data (1-2 fetuses in 1-2 litters). Furthermore, a higher incidence of this fetal variation (3 fetuses in 3 litters) was observed at 10 mg/kg/day and was not statistically significant, supporting the spurious nature of this finding. No other test substance-related fetal alterations were observed at any dose level. Fetal viability, sex ratio and litter size were comparable across all groups. Thus, the no-observed effect levels (NOEL) for maternal and developmental toxicity was 10 mg/kg/day.

In a 90-day feeding and one-generation reproduction study previously conducted in rats, the number of pups per litter at birth was decreased at 400 ppm in the presence of decreased maternal body weights, body weight gain and food efficiency. The NOEL for that study was 100 ppm. Dietary levels of 100 and 400 ppm corresponded to an average daily intake of 8 and 31 mg/kg/day, respectively, for female rats. Thus, the developmental/reproductive toxicity was observed at similar dose levels in both studies (30 mg/kg/day), and the NOELs were similar (8 and 10 mg/kg/day).

Under these experimental conditions, the findings described above appear to be reportable, based upon guidance given in the EPA TSCA Section 8(e) Reporting Guide (June, 1991). However, we do not believe these findings represent a unique hazard to the conceptus.

Sincerely,



A. Michael Kaplan, Ph.D.
Director – Regulatory Affairs and Occupational Health

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